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(54) Title: SUSTAINED RELEASE DELIVERY OF HIGHLY WATER–SOLUBLE COMPOUNDS

(57) Abstract

The invention is an oral pharmaceutical composition comprising a) a tablet core comprising a therapeutically effective amount of a water–soluble active ingredient, or a phamaceutically acceptable salt thereof, a water swellable polymer capable of swelling upon hydration, and a neutralizing agent which modulates hydration and provides for release of the active ingredient from the tablet core into the gastrointestinal tract by extrusion of swelling polymer, said swelling polymer containing the active ingredient, from the core, and b) a water insoluble film coating material surrounding the tablet, wherein the composition has a plurality of apertures which provide a means for the active ingredient to leave the core unimpeded by the film wherein the composition facilitates controlled dual release of the active ingredient from the tablet core into the gastrointestinal tract by diffusion directly from the core and by extrusion of swelling polymer from the core.

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TITLE OF THE INVENTION

SUSTAINED RELEASE DELIVERY OF HIGHLY WATER-SOLUBLE COMPOUNDS

BACKGROUND OF THE INVENTION

The invention relates to compositions which provide sustained release of highly water-soluble compounds, including those which are highly water-soluble at low pH.

Highly water-soluble compounds are often released quickly in the gastrointestinal tract, leading to sharp increases and subsequent decreases in plasma level concentrations. Sustained release formulations have been prepared in a number of ways, generally to protect the active ingredient from exposure to stomach contents, and possibly intestine contents, as well, until the desired time of release. Typical of such formulations is the one described in United States Patent 5,171,580 ('580).

The '580 patent is concerned with a small, three layered sustained release formulation that provides targeted delivery of a cancer drug to the colon, the site where drug release is desired. After the '580 compositions pass from the stomach into the intestine, three layers must dissolve before the drug is absorbed: the outer gastro-resistant coating, which will begin to dissolve once exposed to upper intestine pH of about 5.5; the intermediate gelling layer which swells and builds up a thick gel layer, allowing for delay in the dissolution of the formulation while the formulation is transported down the intestinal path, and; the inner anionic copolymer layer which is soluble at a pH above 7, ensuring drug release in the lower part of the intestinal tract. At column 8, lines 47-55, the '580 patent states that, following administration to a patient, the tablets cover the whole length of the small bowel within 10 hours, without significant changes of the coating and no drug release. Drug is released only in the caecum and colon, when the tablets start to disintegrate. The formulations described in the '580 patent do not release drug in an acidic environment.

United States Patent 4,839,177 describes a tablet having a) a deposit core which includes the active ingredient, between 5 and 80% of a crosslinked insoluble swellable polymer such as sodium carboxymethylcellulose or an acrylate, and between 90 and 10% of a gellable polymer such as methylcellulose, carboxymethylcellulose or a glycol, and b) a support platform including a polymeric insoluble material such as a cellulose or acrylate. The polymeric insoluble material also optionally coats the deposit core to modify release properties. The tablet relies on the swelling force of the swellable polymer to control the release of the active

ingredient. Swelling force is increased with increasing amounts of swellable polymer and decreases with increasing amounts of gellable polymer. These formulations have the disadvantage of being unable to effectively control release of highly water-soluble active ingredients.

United States Patent 4,218,433 describes a tablet having a hollowed portion of specified dimensions which affects elution of water-soluble, slightly water-soluble or water insoluble active ingredient from the tablet. The tablet with the hollowed out portion is coated with an agent that is insoluble in water, water permeable, and soluble in organic solvents, e.g., methacrylic acid ester copolymer. When the tablet is coated, a small space is formed between the film formed by the coating material and the hollow surface portion. The film becomes porous to allow the active ingredient to elute out at a constant rate. If the hollow is smaller that the specified dimensions, the active ingredient won't be eluted from the hollow, and if the hollow is larger than the specified dimensions, the hollow becomes covered with the coating film.

United States Patent 5,366,738 ('738) discloses a device which consists essentially of a homogeneous compressed core prepared from an admixture comprising a therapeutically effective amount of a pharmaceutically active ingredient, and a polymer which forms microscopic gelatinous beads upon hydration. The core is coated with a water insoluble, water impermeable polymeric coating, which surrounds and adheres to the core, the coating having a plurality of apertures, exposing between about 5 and about 75% of the core surface. While '738 describes a means for controlling release of an insoluble pharmaceutically active ingredient contained within the gelatinous beads, it does not distinguish a polymer hydration modulating agent which is suitable for delivery of highly water-soluble active ingredients, the release rate of which is governed by both diffusion and extrusion mechanisms.

The compositions of the present invention solve the difficult problem of providing sustained plasma level concentration of highly water-soluble active compounds. The compositions of the invention acts to control release of the highly water-soluble active ingredient by regulating both diffusion and extrusion of the active ingredient.

SUMMARY OF THE INVENTION

The invention is an oral pharmaceutical composition comprising a) a tablet core comprising a therapeutically effective amount of a water-soluble active ingredient, or a pharmaceutically acceptable salt thereof, a water swellable polymer capable of swelling upon hydration, and a neutralizing agent which modulates hydration and provides for release of the active ingredient from the tablet core into the gastrointestinal tract by extrusion of swelling polymer, said polymer containing the active ingredient, from the core, and

b) a water insoluble film coating material surrounding the tablet, wherein the composition has a plurality of apertures which provide a means for the active ingredient to leave the core unimpeded by the film,

wherein the composition facilitates controlled dual release of the active ingredient from the tablet core into the gastrointestinal tract by diffusion directly from the core and by extrusion of swelling polymer from the core.

In one class of compositions, the tablet core comprises an amount of active ingredient of between about 0.01% to 75% by weight of the total core mass, an amount of neutralizing agent between about 0.01% to 75% by weight of the total core mass, and an amount of gel forming polymer between about 5 to 75% by weight of the total core mass.

In a group of the class of compositions, the active ingredient has a solubility in water of at least 1 part active ingredient per 50 parts water.

The invention also comprises a method for orally administering, to a patient, a therapeutically effective dose of a highly water-soluble active ingredient in a pharmaceutical composition core comprising ahighly water-soluble active ingredient, a water swellable polymer capable of swelling upon hydration, and a neutralizing agent which modulates hydration and provides for release of the active ingredient from the tablet core into the gastrointestinal tract by extrusion of swelling polymer, said polymer containing the active ingredient, from the core, wherein said core is coated with a water insoluble film coating material surrounding the tablet, and wherein said composition has a plurality of apertures which provide a means for the active ingredient to leave the core unimpeded by the film, wherein the composition facilitates controlled dual release of the active ingredient from the tablet core into the gastrointestinal tract by diffusion directly from the core and by extrusion of swelling polymer from the core, which comprises releasing the dose to the gastrointestinal system by two means, wherein a first means is diffusion, directly from the core, of

active ingredient into the gastrointestinal system of the patient, and a second means is extrusion, from the core, of swelling polymer comprising active ingredient into the gastrointestinal system.

The ratio of polymer and neutralizing agent governs the release rate of the highly water-soluble active ingredient. The ratio of polymer to neutralizing agent ranges between 0.01:1 and 100:1.

DETAILED DESCRIPTION OF THE INVENTION

The invention is a pharmaceutical composition comprising a) a tablet core comprising a therapeutically effective amount of a water-soluble active ingredient, or a pharmaceutically acceptable salt thereof (also referred to herein as the "active ingredient"), a water swellable polymer capable of swelling upon hydration, and a neutralizing agent which modulates hydration and provides for release of the active ingredient from the tablet core into the gastrointestinal tract by extrusion of swelling polymer, and b) a water insoluble film coating material surrounding the tablet, wherein the composition has a plurality of apertures exposing between about 1 and about 75% of the core surface to the environment of use, wherein the composition facilitates controlled dual release of the active ingredient from the tablet core into the gastrointestinal tract by diffusion directly from the core and by extrusion of swelling polymer from the core. The tablet may also contain other tablet excipients.

The apertures provide controlled release from the tablet core comprising the highly water-soluble active ingredient. The apertures provide a means for the active ingredient to leave the core unimpeded by the film. The rate of release is regulated by the rate of diffusion of the active ingredient directly from the tablet core composition and the rate of extrusion of active ingredient with the swelling polymer.

Compositions of the invention are useful in the manufacture of a medicament for sustained release of a water-soluble active ingredient.

In operation, aqueous solution from the environment of use (e.g., gastrointestinal system) contacts the surface of the core that is exposed within the apertures. The available water begins to hydrate the polymer at the surface of the

core. The neutralizing agent, at the exposed core surface, is solubilized and establishes the environment required for control of polymer hydration.

As the polymer particles are hydrated, the swelling polymer moves from the surface. At the same time, the swelling polymer moves a portion of the active ingredient from the surrounding surface by extrusion into the environment. The swelling polymer moves from the core surface into the environment of use in a dispersion. Another portion of the active ingredient moves from the core into the environment by diffusion. As a result, controlling the surface area of the core which is exposed to the environment of use, the portion of active ingredient moved into the environment by the swelling polymer, and the portion of active ingredient diffused directly into the environment, effectively controls the delivery rate of medicament to the environment.

Neutralizing agent which modulates hydration and provide for release of the active ingredient from the tablet core into the gastrointestinal tract by extrusion of swelling polymer neutralizes the polymer, which upon hydration forms swelling polymer. The neutralizing agent thereby regulates gel formation at a rate which allows for a portion of the highly water-soluble active ingredient to become integrated within the gel matrix formed by the polymer, and allows for another portion to freely move from the core directly into the aqueous environment. Delivery of the active ingredient occurs from the surface of the core and from within the core so that the delivery rate is dependent on diffusion of the active ingredient from inside the core to the environment of use as well as extrusion of the swelling polymer, containing the active ingredient, from the core. In one class of compositions of the invention, the neutralizing agent is selected from the group consisting of sodium phosphate dibasic, potassium phosphate, and sodium citrate.

Other features and advantages of the invention will be apparent to those skilled in the art from the following detailed description of the invention.

By "drug delivery device" is meant, a dosage form that provides a convenient means of delivering a pharmaceutically active ingredient or drug to a subject in need thereof. The subject can be a human or any other animal in need of such pharmaceutically active ingredient. The device is designed to be useful for the

delivery of a pharmaceutically active ingredient by any pharmaceutically accepted means such as by swallowing, retaining it within the mouth until the beneficial agent has been dispensed, placing it within the bucal cavity, or the like.

By "controlled" is meant that the rate of release of the pharmaceutically active ingredient, that is the amount of pharmaceutically active ingredient released from the device to the environment of use, follows a predetermined pattern. Thus, relatively constant or predictably varying amounts of the beneficial agent can be dispensed over a specified period of time.

By "pharmaceutically active agent," "active ingredient," "medicament," or "beneficial agent" is meant any highly water-soluble compound commonly referred to as a "drug" and its equivalents which includes any physiologically or pharmacologically active substance that produces a localized or systemic effect or effects in animals. By highly water-soluble is meant a drug which readily solubilizes in water at a pH approaching neutrality. Such compounds may be those which are highly charged and/or highly polar (e.g., those having an ammonium ion or similar positively charged group at ambient pH or a negatively charged groups such as a carboxylate or tetrazole at ambient pH) and/or those incorporating heteroatoms such as oxygen or nitorgen atoms into the molecule. Typical of such compounds are compounds having a solubility of at least 100 mg/ml.

Exemplary active ingredients include antihistamines, antibiotics, anticoagulants, cholinergic agents, antimuscarines, sympathomimetics, cardiac drugs, antihypertesive agents, antiinflammatory agents, opiate agents, tranquilizers, stimulaants, barbiturates, sedatives, expectorants, antiemetics, heavy metal antagonists, muscle relaxants, vitamins, and other classes of drugs having the above-specified solubility profile. Specific examples of such active ingredients which are well known to those skilled in the pharmaceutical arts are carbinoxamine maleate, dexchlorpheniramine maleate, doxylamine succinate, promethazine, tripelenamine citrate, tripelenamine hydrochloride, dicloxacillin sodium, nafcillin sodium, carbenicillin indanyl sodium, clindamycin palmitate hydrochloride, lincomycin hydrochloride, metronidazole hydrochloride, bethanecol chloride, neostigmine bromide, pyridostigmine bromide, hexocyclium methyl sulfate, hyoscyamine sulfate,

oxypehnonium bromide, ephedrine sulfate, pseudoephedrine hydrochloride, diltiazem hydrochloride, procainamide hydrochloride, quinidine gluconate, timolol maleate, tocainide hydrochloride, captopril, meclofenamate sodium, tolmetin sodium, propoxyphene hydrochloride, chlorpromazine hydrochloride, diethylpropion hydrochloride, methylphenidate hydrochloride, phendimetrazine tartrate, phenmetrazine hydrochloride, amylobarbitone sodium, hydroxyzine hydrochloride, potassium iodide, metochlopramide hydrochloride, penicillamine hydrochloride, flavoxate hydrochloride, oxybutynin hydrochloride, thiamine hydrochloride, and etidronate disodium.

Examples of active ingredients of high solubility are set out in the table below. The listed solubilities are in 1 part soluble in so many parts water.

Drug	Aqueous solubility	pKA
Antihistamines		
Azatadine maleate	very soluble	9.3
Brompheniramine maleate	1 in 5	3.59, 9.12
Carbinoxamine maleate	1 in 1	8.1
Chlorpheniramine maleate	1 in 4	9.2
Dexchlorpheniramine maleate	1 in 1.1	
Diphenhydramine hydrochloride	1 in 1	9.0
Doxylamine succinate	1 in 1	5.8, 9.3
Methdilazine hydrochloride	1 in 2	7.5
Promethazine	1 in 0.6	9.1
Trimeprazine tartrate	1 in 4	
Tripelennamine citrate	1 in 1	3.9, 9.0
Tripelennamine hydrochloride	1 in 1	
Triprolidine hydrochloride	1 in 2	3.6, 9.0
Antibiotics		
Penicillin V potassim	1 in 1.5	0.5
Cloxacillin sodium	1 in 2.5	2.7
Dicloxacillin sodium	freely soluble	2.7

Nafcillin sodium	freely soluble	2.7
Oxacillin sodium	1 in 3.5	2.8
Carbenicillin indanyl sodium	freely soluble	2.6, 2.7, 3.3
Oxytetracycline hydrochloride	1 in 2	3.3, 7.3, 9.1
Tetracycline hydrochloride	1 in 10	3.3, 7.7, 9.7
Clindamycin phosphate	1 in 2.5	7.7
Clindamycin hydrochloride	1 in 2	7.7
Clindamycin palmitate hydrochloride	freely soluble	
Lincomycin hydrochloride	1 in 1	7.6
Novobiocin sodium	1 in 5	4.2, 9.1
Nitrofurantoin sodium	soluble	7.2
Metronidazole hydrochloride	1 in 1	2.6
Antituberculosis Agents		
Isoniazid	1 in 8	1.8, 3.5, 10.8
Cholinergic Agents		
Ambenonium chloride	1 in 5	
Bethanecol chloride	1 in 1	
Neostigmine bromide	1 in 0.5	12.0
Pyridostigmine bromide	1 in 1	
Antimuscarinics		
Anisotropine methylbromide	soluble	
Clidinium bromide	soluble	
Dicyclomine hydrochloride	1 in 20	9
Glycopyrrolate	1 in 5	
Hexocycliym methylsulfate	freely soluble	
Homatropine methylbromide	1 in 6	9.9
Hyoscyamine sulphate	2 in 1	3.5
Methantheline bromide	1 in 5	

Hyoscine hydrobromide	1 in 3	7.6
Oxyphenonium bromide	freely soluble	3.2
Propantheline bromide	very soluble	9.0
Tridihexethyl chloride	1 in 3	
Sympathomimetics		
Bitolterol mesylate		9.1
Ephedrine	1 in 20	9.6
Ephedrine hydrochloride	1 in 3	9.6
Ephedrine sulphate	1 in 1	9.6
Orciprenaline sulphate	1 in 2	9.0, 10.1, 11.4
Phenylpropanolamine hydrochloride	1 in 2.5	9
Pseudoephedrine hydrochloride	1 in 1	9.8
Ritodrine hydrochloride	1 in 10	9
Salbutamol sulphate	1 in 4	9.3, 10.3
Terbutaline sulphate	1 in	8.7, 10.0, 11.0
Sympatholytic Agents		
Phenoxybenzamine hydrochloride	1 in 25	4.4
Miscellaneous Autonomic Drugs		
Nicotine	soluble	7.9
Iron Preparations		
Ferrous gluconate	1 in 10	
Ferrous sulphate	1 in 5	
Haemostatics		
Aminocaproic acid	1 in 1.5	4.43, 10.73
Cardiac Drugs		
Acebutolol hydrochloride	1 in 5	9.4

Diltiazem hydrochloride	freely soluble	7.7
Disopyramide phosphate	1 in 20	8.4
Flecainide acetate	1 in 20	9.3
Procainamide hyrdochloride	1 in 0.25	9.23
Propanolol hydrochloride	1 in 20	9.5
Quinidine gluconate	freely soluble	4.0, 8.6
Timolol maleate	freely soluble	9
Tocainide hydrochloride	freely soluble	7.8
Verapamil hydrochloride	1 in 20	4-6.5
Antihypertensive Agents		
Captopril	freely soluble	3.7, 9.8
Clonidine hydrochloride	1 in 13	8.2
Hydralazine hydrochloride	1 in 20	7.3
Mecamylamine hydrochloride	1 in 5	11.2
Metoprolol tartrate	very soluble	9.68
Vasodilators		
Papaverine hydrochloride	1 in 2	6.4
Non-Steroidal Antiinflammatory Agents		
Choline salicylate	very soluble	
Magnesium salicylate	1 in 13	
Meclofenamate sodium	freely soluble	4.0
Naproxen sodium	soluble	4.15
Tolmetin sodium	freely soluble	3.5
Opiate Agonists		
Codeine hydrochloride	1 in 30	8.2
Codeine phosphate	1 in 4	8.2
Codeine sulfate	1 in 30	8.2
Dextromoramide tartrate	1 in 25	7.1

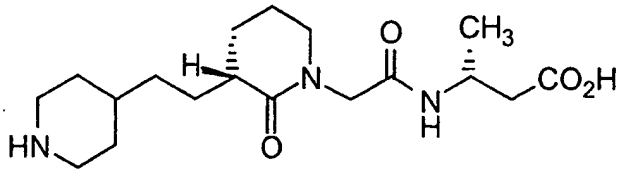
Hydrocodone bitartrate	1 in 10	8.3
Hydromorphone hydrochloride	1 in 3	8.2
Pethidine hydrochloride	very soluble	8.7
Methadone hydrochlorideÎ	1 in 2	8.3
Morphine sulfate	1 in 15.5	8.0, 9.9
Morphine acetate	1 in 2.25	
Morphine lactate	1 in 10	
Morphine meconate	1 in 20	
Morphine nitrate	1 in 1.5	
Morphine monobasic phosphate	1 in 5	
Morphine tartate	1 in 11	
Morphine valerate	1 in 5	
Morphine hydrobromide	1 in 25	
Morphine hydrochloride	1 in 17.5	
Propoxyphene hydrochloride	1 in 0.3	
Anticonvulsants		
Phenobarbital sodium	1 in 3	7.41
Phenytoin sodium	soluble	8.3
Troxidone	1 in 13	
Ethosuximide	1 in 4.5	9.0
Valproate sodium	1 in 5	4.8
Tranquilizers		
Acetophenazine maleate	1 in 10	
Chlorpromazine hydrochloride	1 in 0.4	9.3
Fluphenazine hydrochloride	1 in 10	3.9, 8.1
Prochlorperazine edisylate	1 in 2	3.7, 8.1
Promazine hydrochloride	1 in 1	9.4
Thioridazine hydrochloride	1 in 9	9.5
Trifluoroperazine		

hydrochloride	1 in 2	8.1
Lithium citrate	1 in2	
Molindone hydrochloride	freely soluble	6.9
Thiothixine hydrochloride	1 in 8	
Stimulants		
Benzphetamine hydrochloride	freely soluble	6.6
Dextroamphetamine sulfate	1 in 10	9.9

These active ingredients are disclosed in Remingtonìs Pharmaceutical Sciences, 16th Ed., 1980, published by Mack Publishing Co., Eaton, Pa. and in The Pharmacological Basis of Therapeutics, by Goodman and Gilman, 6th Ed., 1980, published by the MacMillan Company, London and in The Merck Index, 11th Edition, 1989, published by Merck & Co., Rahway, N.J. The dissolved drug can be in various forms, such as charged molecules, charged molecular complexes or ionizable salts. Acceptable salts include, but are not limited to hydrochlorides, hydrobromide, sulfate, laurylate, palmitate, phosphate, nitrate, borate, acetate, maleate, malate, tromethamine, tartrate, oleate, salicylate, salts of metals, and amines or organic cations, for example quaternary ammonium.

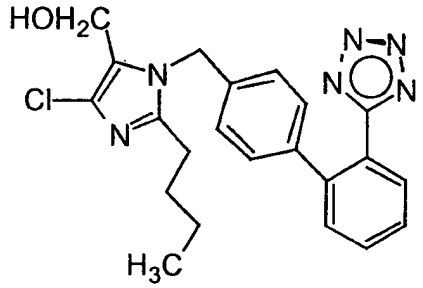
Derivatives of pharmaceutically active ingredients such as esters, ethers and amides without regard to their ionization and solubility characteristics can be used alone or mixed with other compounds. Also, a pharmaceutically active ingredient can be used in a form that upon release from the device, is converted by enzymes, hydrolyzed by body pH or other metabolic processes to the original form, or to a biologically active form. That is, prodrugs are specifically included within the definition of pharmaceutically active ingredients.

United States Patent 5,281,585, describes [3Δ-[2-Piperidin-4-yl)ethyl]-2-piperidone-1]acetyl-3Δ-methyl- -alanine, shown below as



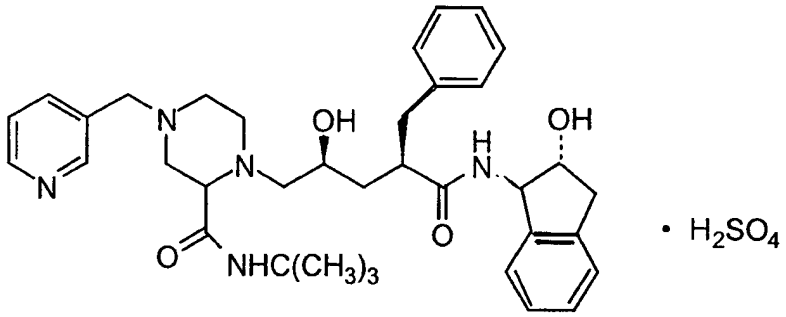
which is a highly water-soluble zwitterionic compound useful for preventing and treating diseases caused by thrombus formation. The compound may be administered to patients where prevention of thrombosis by inhibiting binding of fibrinogen to the platelet membrane glycoprotein complex IIb/IIIa receptor is desired.

United States Patent 5,153,197 describes 2-butyl-4-chloro-1-[p-(o-1H-tetrazol-5-phenyl)-benzyl]imidazole-5-methanol monopotassium salt, shown below as



which is a highly water-soluble acidic angiotensin II receptor antagonist antihypertensive compound.

United States Patent 5,413,999 describes [1(1S,2R),5(S)]-2,3,5-trideoxy-N-(2,3-dihydro-2-hydroxy-1H-inden-1-yl)-5-[2-[[(1,1-dimethylethyl)amino]carbonyl]-4-(3-pyridinylmethyl)-1-piperazinyl]-2-(phenylmethyl)-D-erythro-pentonamide sulfate (1:1) salt, shown below as:



which is a highly soluble inhibitor of the human immunodeficiency virus protease.

Some of the active ingredients included within the compositions of the present invention are chiral; included within the scope of the present invention compositions are those having racemic mixtures and separated enantiomers of the active ingredient. Furthermore, hydrates as well as anhydrous compositions and

polymorphs of the active ingredient may be included in compositions of the present invention.

The term "pharmaceutically acceptable salts" means non-toxic salts of the active ingredients which are generally prepared by reacting the free base with a suitable organic or inorganic acid. Representative salts include the following salts: acetate, benzenesulfonate, benzoate, bicarbonate, bisulfate, bitartrate, borate, bromide, calcium edetate, camsylate, carbonate, chloride, clavulanate, citrate, dihydrochloride, edetate, edisylate, estolate, esylate, fumarate, gluceptate, gluconate, glutamate, glycollylarsanilate, hexylresorcinate, hydrabamine, hydrobromide, hydrochloride, hydroxynapthoate, iodide, isothionate, lactate, lactobionate, laurate, malate, maleate, mandelate, mesylate, methylbromide, methylnitrate, methylsulfate, mucate, napsylate, nitrate, oleate, oxalate, pamaote, palmitate, panthothenate, phosphate/diphosphate, polygalacturonate, salicylate, stearate, subacetate, succinate, tannate, tartrate, teoclate, tosylate, triethiodide, valerate.

The term "animal" includes mammals, humans and primates such as domestic, household, sport or farm animals such as sheep, goats, cattle, horses and pigs, laboratory animals such as mice, rats and guinea pigs, fishes, avians, reptiles and zoo animals.

The compressed core contains a "therapeutically effective amount" of beneficial agent and a polymer which upon hydration results in microscopic gel beads. By "therapeutically effective amount" is meant that the quantity of pharmaceutically active ingredient which has been demonstrated to be sufficient to induce the desired effect during studies utilizing the compound.

Other excipients such as lactose, magnesium stearate, microcrystalline cellulose, starch, stearic acid, calcium phosphate, glycerol monostearate, sucrose; polyvinylpyrrolidone, gelatin, methylcellulose, sodium carboxymethylcellulose, sorbitol, mannitol, polyethylene glycol and other ingredients commonly utilized as stabilizing agents or to aid in the production of tablets may also be present in the layers of the core.

The "swellable polymer" or "swelling polymer" useful in the novel device of this invention broadly encompasses any polymer that upon hydration, is

capable of producing discrete gel beads which support a suspension, including the beneficial agent, as it forms. The term "swellable" implies that the polymer is in a non-hydrated state, while the term "swelling" implies that the polymer is in a hydrated state. The gel forming polymer used also must exude from the core surface in such a way that the beneficial agent is carried into the environment of use. Upon hydration, the gelatinous beads must be predisposed to leave the surface taking the drug with it. This assures a constant surface area exposed to the solvent of the environment of use and maintains the appropriate rate of release.

The "film polymer" useful in the invention, and described more completely below, is a polymeric material which forms the water insoluble film coating material which surrounding the tablet core.

The "gelatinous beads" are composed of discrete particles of hydrated polymer. Both size and hydration rate of these microscopic gel beads are characteristics of the individual polymers. Illustrative of this type of polymer are "AQUAKEEP J-550", "AQUAKEEP J-400", which are trade names for sodium acrylate acrylate polymer produced by Seitetsu Kagaku Co., Ltd., Hyogo, Japan. The "AQUAKEEP" polymers are generically described in United States Patent 4,340,706. Also illustrative of this type of polymer are the carboxypolymethylenes prepared from acrylic acid cross-linked with allyl ethers of sucrose or pentaerythritol and sold under the trade names "CARBOPOL 934P" and "CARBOPOL 974P" which are trade names for two carbamer type polymers produced by B.F. Goodrich Chemical Company, Cleveland, Ohio. Carbamer polymers are generically described in United States Patent 2,909,462 and in the National Formulary XVII at p. 1911, CAS Registry Number 9003-01-4. All of the forgoing references are hereby incorporated by reference.

In the dry state, "CARBOPOL 974P" and "CARBOPOL 934P" particles range in size from 2 to 7 microns. When these particles are hydrated, microscopic gel beads in the range of 20 microns are produced. When "AQUAKEEP J-550" or "AQUAKEEP J-400" particles are hydrated, microscopic gel bead diameter can range in size from 100 to 1000 microns.

By "gelatinous" is meant a semisolid system consisting of hydrated polymer interpenetrated by the aqueous solvent of the environment of use.

By "compressed core" is meant that an admixture of ingredients comprising a beneficial agent, a polymer which produces gelatinous particles when hydrated, neutralizing agent, and other ingredients that may affect any of (1) the rate of production of the dispersion; (2) the stability of the components of the dosage form; or (3) the mixing or compression characteristics of the Admixture, is blended in such a way to produce a uniform material. This uniform material is then compressed, within a die, to produce a desired form, normally in the shape of a tablet, capsule or bolus.

The "neutralizing agent" modulates hydration and provides for release of the active ingredient from the tablet core into the gastrointestinal tract by diffusion directly from the core and by extrusion of swelling polymer. The neutralizing agent is solubilized by the aqueous media of the environment and establishes an environment such that the pH, ionic strength or hydrophilic character is appropriate for the desired polymer gel bead hydration rate.

The active ingredient may be in a layer of the core as a dispersion, particle, granule, or powder. Also, the pharmaceutically active ingredient may be mixed with a binder, dispersant, emulsifier or wetting agent and dyes.

In one embodiment of the tablet core, core drug loading is between about 0.01% to 75% by weight of the total core mass (e.g., between 0.05 nanogram to 5 grams or more, such as 25 ng, 1 mg, 5 mg, 250 mg, 500 mg, 1.5 g), the amount of neutralizing agent is between about 0.01% to 75% by weight of the total core mass, and the amount of gel forming polymer is between about 5 to 75% by weight of the total core mass.

The core compartment containing the drug, the neutralizing agent and gelatinous microscopic particle polymer as described herein, is typically in the form of a solid conventional tablet. Generally, the core is compressed into its final shape using a standard tablet compressing machine. The core may contain compressing aids and diluents such as lactose that assist in the production of compressed tablets. The core can be comprised of a mixture of agents combined to give the desired

manufacturing and delivery characteristics. The number of agents that be combined to make the core is substantially without an upper limit with the lower limit equaling three components: the gelatinous forming polymer, the beneficial agent, and neutralizing agent.

Once the core is prepared, it can be coated and drilled in the manner described.

In instances where the pharmaceutically active ingredient, the gel forming polymer and neutralizing agent exhibit the desired release rate, stability, and manufacturing characteristics, there is no critical upper or lower limit as to the amount of pharmaceutically active ingredient that can be incorporated into a layer of the core. The ratio of drug to excipient is dictated by the desired time span and profile of release, and the pharmacological activity of the drug.

Once the composition is within the environment of use, the polymer of the compressed core which is exposed to the ambient aqueous solution at the coating apertures begins to hydrate and produce gelatinous microscopic particles. By "in situ production and release of a dispersion" is meant that during the production of the swelling polymer, soluble and insoluble core components located near the polymer particles become dispersed and mixed in such a manner that a gelatinous dispersion is produced. The dispersion moves a portion of the active ingredient from the core into the aqueous solvent, bringing the beneficial agent into the environment of use. Another portion of active ingredient move into the environment free of interaction with the swelling polymer.

The coating, applied to the core of the invention, is a material that is insoluble in the environment of use, can form films, and does not adversely affect the pharmaceutically active ingredient, animal body, or host. The coating is insoluble in water and impermeable to the selected product, drugs, neutralizing agent, or to other compounds in the device. This material is insoluble in body fluids and non-erodible or it can be bioerodible after a predetermined period with bioerosion following the end of the active drug release period. In each instance, it is insoluble to solvent and solute(s) found in the environment of use and is suitable for construction of the device.

The polymeric coating is applied to and adheres to the entire surface of the core. Apertures are cut in the coating to expose the core, using either a mechanical or laser drill, a coring device or any other pharmaceutically accepted means. In one embodiment, a mechanical drill is used to produce the apertures. In another embodiment, a laser is used to make the apertures.

The apertures allow solution to make contact only with exposed portions of the core when in use. The number, size and configuration of the apertures is chosen to provide the release rate required to suit a pharmacologically recognized requirement since the hydration of the polymer will occur only where the apertures allow such core-solvent contact.

The coating can be applied by dipping the cores into a suitable solution of the film polymer or by spray coating the cores with the film polymeric solution. Among the film polymers that can provide this type of protection are cellulose acetate butyrate, polyvinyl chloride, and ethyl cellulose. In addition, other materials such as plasticizers may be included with the coating to enhance its stability, color, elasticity, ease of application or opacity, provided that these ingredients do not reduce the impermeability or insolubility of the coating. Similarly, compounds such as triethylcitrate may be added to the coating.

The coating is applied to a thickness of from about 1 to about 1000 microns but preferably about 10 to about 500 microns typically, although thinner and thicker coatings fall within the scope of the invention.

The expression "aperture" as used herein, refers to ports through the coating which expose the surface of the core to the environment. The size and number of apertures is chosen to effect the desired release rate. In determining the aperture size and number, the hydration rate of the gel forming polymer, the type and concentration of the neutralizing agent used in the core and the ability of the beneficial agent to form ions must be considered. The apertures are generally positioned in a regular pattern on both faces of the device although they can be positioned anywhere on the core including the edges or as previously described, on one face. The apertures are generally circular but may be of any design that results in the proper release rate. When the aperture is circular, its diameter ranges from about

0.1 mm to about 5 mm with diameters of about 0.3 to about 3.5 mm typical. The number of apertures may be between 2 and 1000, typically between 5 and 100.

The apertures may be made by drilling the appropriate size hole through the coating using a mechanical or laser based process. In the preferred embodiment, a digital laser marking system is used to drill the holes required. This system allows for an array of apertures to be drilled on both faces of a dosage form simultaneously and at rates suitable for production of dosage forms.

The steps involved in the laser drilling process are as follows: a digital laser marking system is focused at a laser stage; the dosage form is moved onto the laser stage of the digital laser marking system; the digital laser marking system is pulsed to energize those laser tubes needed to drill the desired apertures along a linear array on the dosage form; the dosage form is moved forward on the laser stage and the digital laser marking system is again pulsed as needed to produce an additional linear array of apertures. The dosage form is then removed from the laser stage.

One embodiment of the insoluble film includes a mixture of eight parts by weight of cellulose acetate butyrate, two parts by weight of cellulose acetate and one part by weight of diethylphthalate. This mixture is dissolved in a solution of methylene chloride and methanol (3:1 v/v) and sprayed onto the cores to a thickness of about 250 microns. Another preferred coating consists of five parts by weight of cellulose acetate butyrate and one part by weight of triethyl citrate dissolved in a mixture of acetone and methanol (3:1 v/v). This mixture is sprayed on the core or the cores are dipped into the mixture so that a coating of about 100 microns is applied.

In a preferred embodiment of the impermeable wall a mixture of ten parts by weight of cellulose acetate butyrate and one part by weight of triethylcitrate is used. This mixture at 3% w/v is dissolved in a solution of acetone and ethanol (3:1 v/v) or methylene chloride and methanol (3:1 v/v) and sprayed onto the cores to a thickness of about 100 microns.

The film polymers used in the coating which are herein described are known to the art or can be prepared according to the procedures in the Encyclopedia of Polymer Science and Technology, Vol. 3, published by Interscience Publishers,

Inc., New York, in Handbook of Common Polymers by Scott, J. R. and Roff, W. J., 1971, published by CRC Press, Cleveland, Ohio.

The following examples illustrate the preparation of the drug delivery device of this invention and their controlled release of one or more therapeutically active ingredients into an environment of use and as such are not to be considered as limiting the invention set forth in the claims appended hereto.

The dosage regimen utilizing the compositions of the present invention is selected in accordance with a variety of factors including type, species, age, weight, sex and medical condition of the patient; the severity of the condition to be treated; the route of administration; the renal and hepatic function of the patient; and the particular active ingredient or salt thereof employed. An ordinarily skilled physician or veterinarian can readily determine and prescribe the effective amount of the drug required to prevent, counter, or arrest the progress of the condition.

In the following examples, [3Δ-[2-Piperidin-4-yl)ethyl]-2-piperidone-1]acetyl-3Δ-methyl-ß-alanine is used as a model drug. The drug is highly effective in the inhibition of platelet aggregation in humans. The aqueous solubility of the drug is greater than 500 mg/ml at 20 degrees C.

EXAMPLE 1

Compositions containing 2, 25 or 100 mg of [3Δ-[2-Piperidin-4-yl)ethyl]-2-piperidone-1]acetyl-3Δ-methyl-ß-alanine

Tablet cores containing 2, 25 or 100 mg respectively, of the compound [3Δ-[2-Piperidin-4-yl)ethyl]-2-piperidone-1]acetyl-3Δ-methyl-ß-alanine are prepared as illustrated below.

		Amount (mg)	
Tablet Ingredients	1a	1b	1c
[3Δ-[2-Piperidin-4-yl)ethyl]-2-piperidone-1]acetyl-3Δ-methyl-ß-alanine	2.0	25.0	100
Sodium phosphate dibasic anhydrous	36	24	12
Avicel PH 101 (Microcrystalline cellulose)	72	50	24.5
Carbopol	12	12	12
Magnesium stearate	0.3	0.3	1.5
Film Coating Ingredients		Amount (mg)	
Cellulose acetate butyrate	13.6	13.6	20.0
Triethyl citrate	1.36	1.36	2.0

[3Δ-[2-Piperidin-4-yl)ethyl]-2-piperidone-1]acetyl-3Δ-methyl-ß-alanine, microcrystalline cellulose, Carbopol, sodium phosphate and magnesium stearate are placed in a V blender and mixed for 5 minutes, compacted into ribbons and milled. The milled material is lubricated with magnesium stearate and compressed into tablets.

The cores are coated with the impermeable wall a mixture of twenty parts by weight of cellulose acetate butyrate and three parts by weight of triethylcitrate. This mixture, at 3% w/v, is dissolved in a solution of acetone and

ethanol (3:1 v/v) and sprayed onto the cores to a thickness of about 100 microns, using a Freund Model HCT-Mini Hi-Coater (pan).

Two hole configurations are evaluated: 44 x 0.5 mm holes drilled in the face of the device which allow for exposure of the core layer which contains the pharmaceutically active ingredient, and 22 x 0.5 mm holes in the face of the device adjacent to the layer which contains the pharmaceutically active ingredient.

EXAMPLE 2

Compositions containing 100 or 75 mg of [3Δ-[2-Piperidin-4-yl)ethyl]-2-piperidone-1]acetyl-3Δ-methyl-ß-alanine

Tablet cores containing 100 or 75 mg respectively, of the compound [3Δ-[2-Piperidin-4-yl)ethyl]-2-piperidone-1]acetyl-3Δ-methyl-ß-alanine were prepared as illustrated below.

Tablet Ingredients	Amount (mg)		
	2a	2b	2c
[3Δ-[2-Piperidin-4-yl)ethyl]-2-piperidone-1]acetyl-3Δ-methyl-ß-alanine	100	100	75
Sodium phosphate dibasic anhydrous	24	36	36
Avicel PH 101 (Microcrystalline cellulose)	12.5	0.5	19.5
Carbopol 974 NF	12	12	18
Magnesium stearate	1.5	1.5	1.5
Film Coating Ingredients	**Amount (mg)**		
Cellulose acetate butyrate	13.6	13.6	20.0
Triethyl citrate	1.36	1.36	2.0

[3Δ-[2-Piperidin-4-yl)ethyl]-2-piperidone-1]acetyl-3Δ-methyl-ß-alanine, microcrystalline cellulose, Carbopol, sodium phosphate and magnesium stearate are placed in a V blender and mixed for 5 minutes, compacted into ribbons and milled. The milled material is lubricated with magnesium stearate and compressed into tablets.

The cores are coated with the impermeable wall a mixture of twenty parts by weight of cellulose acetate butyrate and three parts by weight of triethylcitrate. This mixture, at 3% w/v, is dissolved in a solution of acetone and

ethanol (3:1 v/v) and sprayed onto the cores to a thickness of about 100 microns, using a Freund Model HCT-Mini Hi-Coater (pan).

Two hole configurations are evaluated: 44 x 0.5 mm holes drilled in the face of the device which allow for exposure of the core layer which contains the pharmaceutically active ingredient, and 22 x 0.5 mm holes in the face of the device adjacent to the layer which contains the pharmaceutically active ingredient.

In vitro release rate performance was measured at 37°C in 0.1 N HCl solution (pH=1.0) and USP water and paddle speed of 50 rpm. Samples were collected and assayed for active ingredient content by HPLC method.

A fourth formulation (2d) containing no sodium phosphate but otherwise being similar in composition to Example 2a was prepared. A comparison of drug release rate of these formulations at pH 6.7 is instructive for observing the effect of increased sodium phosphate levels on drug release. The ratio of polymer:sodium phosphate for each formulation is as follows: 2a (1:1), 2b (1:2), 2c (1:3) and 2d (1:0).

	% drug released at pH 6.7			
Time (hours)	2d (1:0)	2a (1:1)	2b (1:2)	2c (1:3)
2	30	33	38	52
4	58	64	71	80
6	79	85	86	89
8	90	92	93	92
10	92	96	93	92
12	95	96	93	92
14	95	96	93	92

The release rate was increased by the presence of sodium phosphate.

WHAT IS CLAIMED IS:

1. An oral pharmaceutical composition comprising

a) A tablet core comprising a therapeutically effective amount of a water-soluble active ingredient, or a pharmaceutically acceptable salt thereof, a water swellable polymer capable of swelling upon hydration, and a neutralizing agent which modulates hydration and provides for release of the active ingredient from the tablet core into the gastrointestinal tract by extrusion of swelling polymer, said polymer containing the active ingredient, from the core, and

b) A water insoluble film coating material surrounding the tablet, wherein the composition has a plurality of apertures which provide a means for the active ingredient to leave the core unimpeded by the film,

wherein the composition facilitates controlled dual release of the active ingredient from the tablet core into the gastrointestinal tract by diffusion directly from the core and by extrusion of swelling polymer from the core.

2. A composition of claim 1, wherein the neutralizing agent is selected from the group consisting of sodium phosphate dibasic, potassium phosphate, and sodium citrate.

3. A composition of claim 2, wherein the tablet core comprises an amount of active ingredient of between about 0.01% to 75% by weight of the total core mass, an amount of neutralizing agent between about 0.01% to 75% by weight of the total core mass, and an amount of swellable polymer between about 5 to 75% by weight of the total core mass.

4. A composition of claim 3 wherein the ratio of swellable polymer to neutralizing agent is between about 0.01:1 and 100:1.

5. A composition of claim 4, wherein the active ingredient has a solubility in water of at least 1 part active ingredient in 50 parts water.

6. A method for orally administering, to a patient, a therapeutically effective dose of a highly water-soluble active ingredient in a pharmaceutical composition core comprising an active ingredient, a water swellable

polymer capable of swelling upon hydration, and a neutralizing agent which modulates hydration and provides for release of the active ingredient from the tablet core into the gastrointestinal tract by extrusion of swelling polymer, said swelling polymer containing the active ingredient, from the core, wherein said core is coated with a water insoluble film coating material surrounding the tablet, and wherein said composition has a plurality of apertures which provide a means for the active ingredient to leave the core unimpeded by the film, wherein the composition facilitates controlled dual release of the active ingredient from the tablet core into the gastrointestinal tract by diffusion directly from the core and by extrusion of swelling polymer from the core, which comprises releasing the dose to the gastrointestinal system by two means, wherein a first means is diffusion, directly from the core, of active ingredient into the gastrointestinal system of the patient, and a second means is extrusion, from the core, of swelling polymer comprising active ingredient into the gastrointestinal system.

7. A method of claim 6, wherein the rate of delivery of the active ingredient to the patient is regulated by both the rate of diffusion of the active ingredient directly from the core and the rate of extrusion of the swelling polymer.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/25063

A. CLASSIFICATION OF SUBJECT MATTER
IPC(6) :A61K 9/28, 9/32, 9/36
US CL :424/468, 472, 473, 474, 480, 482
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 424/468, 472, 473, 474, 480, 482

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 4,439,195 A (SWANSON et al) 27 March 1984, see column 5, line 45 through column 10, line 43.	1-7
Y	US 5,120,548 A (McCLELLAND et al) 09 June 1992, see column 2, lines 30-39, column 3, lines 3-26, column 3, line 67 through column 6.	1-7
Y	US 5,654,005 A (CHEN et al) 05 August 1997, see column 3, line 44 through column 5, line 23.	1-7

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 05 JANUARY 2000	Date of mailing of the international search report 24 February 2000
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